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(71) Applicant (*for all designated States except US*): SARISSA INC. [CA/CA]; 121 Timber Drive, London, Ontario N6K 4A2 (CA).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KOROPATNICK, D., James [CA/CA]; c/o London Regional Cancer Center, 790 Commissioners Road East, London, Ontario N6A 4L6 (CA). VINCENT, Mark, D. [CA/CA]; c/o London Regional Cancer Center, 790 Commissioners Road East, London, Ontario N6A 4L6 (CA).

(74) Agent: MBM & CO.; P.O. Box 809, Station B, Ottawa, Ontario K1P 5P9 (CA).

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/086416 A1

(54) Title: COMBINATIONS OF ANTISENSE OLIGONUCLEOTIDES DIRECTED AGAINST THYMIDYLATE SYNTHASE mRNA AND USES THEREOF

(57) Abstract: Effective combinations of antisense oligonucleotides directed against thymidylate synthase mRNA are provided for use in cancer therapies. Combinations of antisense oligonucleotides have enhanced activity compared to the activity of the individual antisense oligonucleotides when used alone. The combinations may be used in conjunction with one or more chemotherapeutic agents to enhance the effects of the chemotherapeutic(s). Such antisense oligonucleotide combinations constitute improved antisense therapies with application to a variety of cancers or proliferative disorders, including drug resistant cancers.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 0480

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/70 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
 IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, SEQUENCE SEARCH, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BERG RANDAL W ET AL: "Combination of two antisense oligodeoxynucleotides targeting thymidylate synthase (TS) maximizes cytotoxicity of TS-directed chemotherapeutics." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 42, March 2001 (2001-03), page 727 XP001154120 92nd Annual Meeting of the American Association for Cancer Research; New Orleans, LA, USA; March 24-28, 2001, March, 2001 ISSN: 0197-016X the whole document</p> <p>—</p> <p style="text-align: center;">-/—</p>	1-15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 August 2003

Date of mailing of the International search report

21/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Morawetz, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERG RANDAL W ET AL: "A 'combination antisense' oligonucleotide strategy to downregulate thymidylate synthase: Two oligos are better than one." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 577 XP001154122 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X the whole document ----	1, 4-9, 12-14
Y	FERGUSON PETER J ET AL: "Antisense down-regulation of thymidylate synthase to suppress growth and enhance cytotoxicity of 5-FUDR, 5-FU and Tomudex in HeLa cells." BRITISH JOURNAL OF PHARMACOLOGY, vol. 127, no. 8, August 1999 (1999-08), pages 1777-1786, XP002250280 ISSN: 0007-1188 the whole document ----	2, 3, 10, 11, 15
Y	BERG RANDAL W ET AL: "Tumor growth inhibition in vivo and G2/M cell cycle arrest induced by antisense oligodeoxynucleotide targeting thymidylate synthase." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 298, no. 2, August 2001 (2001-08), pages 477-484, XP002250281 ISSN: 0022-3565 the whole document ----	1-15
Y	FERGUSON PETER J ET AL: "Antisense-induced down-regulation of thymidylate synthase and enhanced cytotoxicity of 5-FUDR in 5-FUDR-resistant HeLa cells." BRITISH JOURNAL OF PHARMACOLOGY, vol. 134, no. 7, December 2001 (2001-12), pages 1437-1446, XP002250282 ISSN: 0007-1188 the whole document ----	1-15
Y	WO 99 63114 A (DEAN NICHOLAS ;ISIS PHARMACEUTICALS INC (US)) 9 December 1999 (1999-12-09) examples 1-6 ----	1-15
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 0480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 15648 A (KOROPATNICK DONALD JAMES ; VINCENT MARK DAVID (CA); ZENECA LTD (GB)) 1 April 1999 (1999-04-01) the whole document ----	1-15
Y	WO 98 49287 A (HYBRIDON INC) 5 November 1998 (1998-11-05) the whole document ----	1-15
T	BERG RANDAL W ET AL: "A "combination oligonucleotide" antisense strategy to downregulate thymidylate synthase and decrease tumor cell growth and drug resistance." CANCER GENE THERAPY, vol. 10, no. 4, 20 April 2003 (2003-04-20), pages 278-286, XP002250283 ISSN: 0929-1903 the whole document -----	

INTERNATIONAL SEARCH REPORTInternational Application No.
PCT/03/00480**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7–11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/05480

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9963114	A 09-12-1999	US AU WO	6087489 A 4224999 A 9963114 A1	11-07-2000 20-12-1999 09-12-1999
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